REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 68-72, 75, 75, 77, 78, 80-82, 84, 86-91 are now pending in this application. Support for the amendment "suitable for administration in vivo" in claim 68 is found at page 13, lines 1-5; support for the amendment "wherein said exogenous loop replaces a removed surface loop in said entity or is inserted between two regions of secondary structure in said entity or between a domain of secondary structure and a terminus of said entity" in claim 68 is found at page 12, lines 27-29; support for the amendment "an odorant or taste receptor of the seven-membrane spanner protein family " in claim 71 is found at page 14, line 2; support for the amendment "endothelial cells of the vasculature, smooth muscle cells of the vasculature " in claim 72 is found at page 18, line 4; support for the amendment " stem cells of the bone marrow" in claim 72 is found at page 18, line 6. New claims 90 and 91 find basis in the application generally. Accordingly, the amendments raise no issue of new matter.

Rejection of Claims 68-72, 74, 75, 77, 78, 80-82, 84, and 86-89 under 35 U.S.C. 112, First Paragraph

The rejection of claims 68-72, 74, 75, 77, 78, 80-82, 84, and 86-89 under 35 U.S.C. 112, First Paragraph as allegedly lacking written description is traversed. The various bases for rejection are separately addressed. Reconsideration is respectfully requested in view of the amendments and remarks.

1) According to the Examiner, the specification does not contemplate placing an exogenous loop at the end of a therapeutic protein. The claims have been amended for the understanding of the Examiner and now recite the requirement that the exogenous loop replace a

removed surface loop in the entity or is inserted between two regions of secondary structure in the entity or between a domain of secondary structure and a terminus of the entity. As amended, the claim does not encompass the insertion of a loop at the end of a protein. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

2) According to the Examiner, the specification does not provide written description for an odorant or taste receptor in claim 71. It is respectfully submitted that such a receptor is described on page 14, line 2 in the context of a seven membrane spanner protein family. Claim 71 has been amended to include this context. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

3) According to the Examiner, the specification does not provide written description for cells of the vasculature such as endothelial cells and smooth muscle cells as recited in claim 72. It is respectfully submitted that the specification provides written description support for endothelial cells and smooth muscle cells in the context of vasculature at page 18, line 4. Claim 72 has been amended to include this context. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

4) According to the Examiner, the specification does provide written description for stem cells of the bone marrow as recited in claim 72. It is respectfully submitted that the specification provides written description support for stem in the context of the bone marrow at page 18, line 6. Claim 72 has been amended to include this context. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 68, 71, 81, 82, 84, and 86 under 35 U.S.C. 102(b) over Wolfson et al.

The rejection of Claims 68, 71, 81, 82, 84, and 86 under 35 U.S.C. 102(b) over Wolfson et al. is respectfully traversed. The examiner asserts that Wolfson teaches an entity (IL-1β) which contains an exogenous surface loop (elastase recognition site). The examiner further asserts that Wolfson et al. discloses that the elastase recognition site maintains its specific binding characteristic and that the mutant IL-1β retains a therapeutic property. The examiner points to the abstract of Wolfson et al. to support these contentions.

Applicants respectfully submit that the Abstract in Wolfson et al, relied by the Examiner is at most an assertion that the IL-1β portion is useful but does not go so far as to suggest that it

retains a therapeutic property. In fact, there is no teaching anywhere in Wolfson demonstrating that the mutant IL-1β retains a therapeutic activity of IL-1β. Wolfson et al. never administered the mutant in vivo and never tested the mutant with cells. Wolfson only demonstrated cleavage by purified enzyme in vitro, which is an experiment that reflects on the structure of the exogenous loop and not on a therapeutic property of the IL-1β.

CD experiments mentioned in Wolfson also do not prove that the IL-1β portion of the mutant has retained a therapeutic activity. In fact, there is a substantial body of evidence teaching that the substitution made by Wolfson et al (replacement of residues 50-53 with a longer loop) has deleterious effects on the activity of IL-1β. For example, Labrolia-Tomkins et al (PNAS vol 88 pgs 11182-11186 1991; copy attached) teaches that mutations of residues proximal to this loop (Phenylalanine 46, Isoleucine 56 and Valine 58) eliminate the ability of IL-1β to bind to its receptor (see Table 3 pg 11184). Moreover, Grutter et al (Protein Engineering vol7 no 5 pp.663-671 1994; copy to be mailed under separate cover) shows that the mutation of the glutamic acid 51 substantially reduces binding affinity for the IL-1β receptor. Thus, knowledge of structure/function of IL-1β teaches that he loop insertion by Wolfson would have negatively impacted therapeutic activity of the IL-1β.

Thus, Wolfson et al, not only fails to demonstrate retention of a therapeutic activity for the IL-1β portion of the mutant but the art strongly supports that such activity would be lacking. Accordingly, the rejection for lack of novelty over Wolfson et al. is without foundation and should be withdrawn.

Rejection of Claims 68-72,74,75,77,78,80-82,84 and 86 under 35 U.S.C. 102(b) over Maeda.

The rejection of Claims 68-72,74,75,77,78,80-82,84 and 86 are being anticipated by Maeda et al. is respectfully traversed.

According to the Examiner, Maeda et al teach that a loop containing the Arg-Gly-Asp sequence inserted into protein A. To support that protein A is a therapeutic entity, the examiner cites to Balint et al.

Maeda et al., however, does not replace a loop in protein A with an RGD loop and does not insert the loop between two regions of secondary structure or between a domain of secondary

structure and a terminus of the protein A, as is required by the claims. Rather, Meada places the loop into one of the two antiparallel alpha helices of protein A (see page 15168, left column, lines 1-4). This means that Maeda placed the loop inside a single secondary structure and not between two regions of secondary structure or between a domain of secondary structure and a terminus as required by the claims.

In addition, although Balint et al. assert that protein A can be administered to an individual for some therapeutic purpose, this idea, more than 15 years of age (see patent filing date), has never to Applicant's knowledge been used for this purpose. Thus, one of ordinary skill would not accept the premise that Protein A is a therapeutic entity intended for therapeutic application in vivo as specified by the claims.

The Examiner's reliance on the use of protein A columns for the therapeutic removal of IgG and IgG-containing immune complexes in the treatment of certain cancers and autoimmune diseases as described in Balint et al. for the rejection also is not availing. In this circumstance, protein A is cited as "perfusion therapy" in which it is used *ex vivo* as a means of removing constituents of blood. This does not meet the requirements in the claims for suitability of in vivo administration.

Thus, the rejection fails because Maeda does not teach or suggest all elements of the invention and Balint is not credible on the question of protein A as a therapeutic entity. Accordingly, the rejection for lack of novelty over Meada et al. is without foundation and should be withdrawn.

In addition to the above arguments, claims 90 and 91 do not read on protein A or its target. Thus, these claims are separately patentable over Maeda.

Rejection of Claims 68-72, 74, 75, 77, 78, 80-82, 84,and 86-89 under 35 U.S.C. §103(a) over Quetermous in view of Rodwell and Barbas

The rejection of Claims 68-72, 74, 75, 77, 78, 80-82, 84,and 86-89 as being obviousness over Quetermous (US Patent 5,811,265) in view of Rodwell (US Patent 5,196,510) and Barbas (1993) is respectfully traversed.

The Quetermous teaches a fusion protein between an immunoglobulin chain and a fibrinolytic enzyme. Fusion proteins like those of Quetermous have nothing to do with the

claimed invention. Thus, the primary reference is wholly off base. Rodwell likewise teaches a fusion protein by adjoining two different protein sequences. This adds nothing to the combination. Finally, Barbas et al teaches a Fab9 antibody in which the heavy chain CDR3 contained a three amino acid "RGD" sequence.

It is unclear from this rejection how the knowledge from each reference is to be combined. Also the rejection fails to demonstrate a motivation to combine these teachings to reach the claimed invention.

The Madison declaration demonstrates nonobviousness of the claimed invention but the Examiner has disregarded it because the claims allegedly read on a therapeutic entity with the loop added to the end of the molecule. Because the claims presently require that the exogenous loop either replace a removed surface loop or be inserted between two regions of secondary structure in said entity or between a domain of secondary structure and a terminus of the entity, the art as combined by the examiner (assuming that it can be combined) does not teach or suggest the invention and all its limitations. Accordingly, the rejection fails to state a *prima facie* case and should be withdrawn.

In addition to the above arguments, claim 91 does not read on an immunoglobulin as the therapeutic entity. Thus, this claim should be separately patentable over this obviousness rejection based on immunoglobulins.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872. If any extensions of time are needed for timely acceptance of papers

submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

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